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INFLAMMATION INDUCES TRANSDIFFERENTIATION OF FIBROBLASTS TO MYOFIBROBLASTS WITH PATHOLOGICAL REMODELLING IN ENDOMYOCARDIAL BIOPSIES OF PATIENTS WITH HFNEF: ONE TRIGGER FOR DIASTOLIC DYSFUNCTION.

ACC Poster Contributions
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Background: The mechanism underlying heart failure with normal EF (HFNEF) are only incompletely understood, but we know that different key mechanisms are involved. One of it is extracellular matrix remodeling, which is known to modulate compliance. Nevertheless, the stimulus for remodeling is still unknown in patients with HFNEF.

Methods: Diastolic dysfunction was analyzed in patients with HFNEF using invasive PV-loops and compared to patients without HFNEF. Endomyocardial biopsies were obtained and analyzed in regard to inflammation and matrix regulation. A human cardiac fibroblast cell culture system derived from HFNEF patients investigated the response of the fibroblasts to different stimuli.

Results: Increased diastolic stiffness was documented in HFNEF patients. In endomyocardial biopsies, we examined increased collagen content which correlated to the diastolic stiffness. Moreover, we documented a decrease in matrix metalloproteinase-1 as well as an increment of the tissue inhibitor, which indicates a down regulation of the collagenase activity. Since those changes can be triggered by inflammatory processes, we investigated cardiac inflammation. Increased numbers of immunocompetent cells (CD3+, CD11a+, CD45+ cells) could be analyzed together with enhanced levels of VCAM-1, as a sign of cardiac inflammation. Interestingly, histological staining revealed that inflammatory cells were the major contributor of increased TGF- β. After stimulation with TGF-β, fibroblasts transdifferentiated into myofibroblasts (α-SMA+), produced more collagen and showed a distinct regulation of MMPs and TIMPs, explaining the low degradation activity. Interestingly, chemokines and TNF- α were also highly expressed after stimulation with TGF-β, explaining the increased transendothelial migration of inflammatory cells.

Conclusions: Tissue inflammation modulates matrix by inducing transdifferentiation of fibroblasts to myofibroblasts, leading to collagen accumulation and a low collagenases activity, known to be an important mechanism for decreased compliance in HFNEF patients. Therefore, targeting inflammation might be a possible future therapy option for HFNEF patients.